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Modulation of Alveolar-Capillary Sodium Handling as a Mechanism of Protection of Gas Transfer by Enalapril, and Not by Losartan, in Chronic Heart Failure

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OBJECTIVES We sought to compare the protective efficacy of enalapril and losartan on lung diffusion in chronic heart failure (CHF).

BACKGROUND In CHF, hydrostatic overload causes disruption of the alveolar-capillary membrane and depression of carbon monoxide diffusion (DCO); enalapril improves DCO through mechanisms still undefined; and saline infusion in the pulmonary circulation worsens DCO, putatively because of an upregulated sodium transport to the alveolar interstitium. We investigated whether enalapril modulates sodium handling and whether losartan shares the same properties.

METHODS In 29 patients with CHF, DCO, its membrane diffusion subcomponent (DM) and right atrial and pulmonary wedge pressures were monitored during saline infusion, in the control condition, during enalapril therapy (20 mg/day) for two weeks and after crossover to losartan (50 mg/day) for two weeks (first 20 patients), or after the combination of enalapril with aspirin (325 mg/day) for one week (last 9 patients).

RESULTS Saline, 150 ml, lowered DCO (−7.9%; $p < 0.01$) and DM (−9.9%; $p < 0.01$) without hydrostatic variations. Responses to 750 ml of saline were qualitatively similar. After treatment with enalapril, baseline DCO ($p < 0.01$) and DM ($p < 0.01$) were augmented; after sodium loading, the percent reductions of DCO ($p < 0.01$) and DM ($p < 0.01$) were comparable to those before it, resulting in higher absolute values. This suggests that the greater the gas conductance improvement with enalapril, the lower the impedance with saline. Losartan was ineffective on gas transfer at rest and under salt challenge. Aspirin counteracted the benefits of enalapril.

CONCLUSIONS In CHF, enalapril protects lung diffusion, possibly through a prostaglandin-mediated modulation of sodium overfiltration to the alveolar interstitium; losartan does not share this ability. (J Am Coll Cardiol 2001;37:398–406) © 2001 by the American College of Cardiology

As chronic heart failure (CHF) progresses, structural alterations of the pulmonary microvascular endothelium and alveolar interstitium develop and are associated with disturbances in gas exchange between blood and alveoli (1–3). Angiotensin-converting enzyme (ACE) inhibition improves, both in the short (3) and long term (4), the pulmonary diffusing capacity for carbon monoxide (DCO) in patients with CHF, but not in normal control subjects, by facilitating the molecular diffusion across the alveolar-capillary membrane (DM component of DCO) (5). Impedance to gas transfer closely correlates with exercise intolerance (2,6) and is refractory to conventional treatment of heart failure and to heart transplantation (7,8). Therefore, two important questions arise: what is the intimate enalapril process? Do type 1 angiotensin receptor (AT_1) blockers share the same properties and mechanisms? As far as ACE inhibitors are concerned, the prostanoid-mediated action of bradykinin (3,9,10) seems to be involved; however, it is unclear whether they affect the structural alterations of the alveolar-capillary membrane, as such, or modulate the functional consequences of these alterations. A disordered salt filtration in the alveolar interstitial space might be an example of functional deterioration. In fact, Puri et al. (11) have reported that 10 ml/kg body weight of 0.9% saline infused in patients in New York Heart Association (NYHA) functional class I caused a depression of DM. Consistently, an amount of saline as small as 150 ml infused in the pulmonary artery of patients in functional class II/III produced a similar effect, without eliciting any hydrostatic variations; also, there was no measurable effect of saline on the lung function of normal control subjects (12). These data have been interpreted as reflecting an upregulation of sodium transport to the alveolar interstitium in patients with CHF, due to remodeling of the capillary wall in response to increased wall stress (13).

We studied DCO, DM and pulmonary capillary blood volume (Vc′) in patients with CHF while they were receiving enalapril and after crossover to losartan. We also

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AT_1 = angiotensin type 1 receptor
CHF = chronic heart failure
DCO = diffusing capacity for carbon monoxide
DM = alveolar-capillary membrane diffusing capacity
HCT = hematocrit
LVEF = left ventricular ejection fraction
NE = norepinephrine
PRA = plasma renin activity
VA = alveolar volume
Vc′ = pulmonary capillary blood volume

investigated the responses of these variables to the infusion of saline in the pulmonary circulation, as well as their variations produced by each of the two drugs.

METHODS

Patients. Male patients were referred to the Institute of Cardiology, University of Milan, for evaluation of CHF. Criteria for inclusion were: 1) chronic stable NYHA functional class II/III due to cardiac dysfunction; and 2) left ventricular ejection fraction (LVEF) ≤40%. Criteria for exclusion were: 1) respiratory or renal disease and airway obstruction; 2) DCO ≤70% of the normal value predicted on the basis of standard nomograms incorporating age, gender, weight and height (14); 3) current or past smoking status (>10 cigarettes/day during one of the past five years); 4) mitral regurgitation exceeding grade 3 on a subjective scale from 0 to 5; and 5) use of ACE inhibitors, AT_1 blockers, acetylsalicylic acid or other cyclo-oxygenase inhibitors within the last two months (3,4,9).

Twenty-nine patients completed the trial. In the first 20 patients (group 1), we investigated the responses to saline in the control condition, while they were taking enalapril and then while taking losartan. In the last nine patients (group 2), we investigated the responses to saline and their variations with enalapril alone and in combination with aspirin. Group 1 comprised 13 patients in NYHA functional class II and seven in class III; 17 of them had idiopathic dilated cardiomyopathy and three had ischemic heart disease. In group 2, five patients were in class II and four were in class III; seven had dilated cardiomyopathy and two had ischemic heart disease. None of these patients had participated in previous studies in our laboratory.

The protocol was approved by the Institution Ethics Committee, and written, informed consent was obtained from each patient. The procedures followed were in accordance with institutional guidelines.

Pulmonary functional evaluation. Vital capacity, total lung capacity and forced expiratory volume in 1 s were assessed with Sensor Medics 2200 Pulmonary Functional Test System (Sensor Medics, Yorba Linda, California). The diffusing capacity for carbon monoxide was determined twice each time, with washout intervals of at least 4 min (the average was taken as the final result), with a standard single-breath technique (15). The measured diffusing capacity was corrected for the patient's hemoglobin concentration. The single-breath alveolar volume (VA) was derived by methane dilution. Then, DCO/VA was calculated to account for the reduction in pulmonary volume in CHF (16) and for hypothetical volume variations with fluid infusion. The diffusing capacities of the alveolar-capillary membrane (DM) and the pulmonary capillary volume of blood available for gas exchange (Vc′) were determined using the classic method described by Roughton and Forster (17). We obtained all measurements with a test gas containing 0.28% carbon monoxide, 14% helium and 21% oxygen, with the balance nitrogen. The DCO measurements were then repeated with a test gas containing 0.3% carbon monoxide, 10% helium and 89.7% oxygen. Studies of reproducibility showed a high level of agreement between consecutive

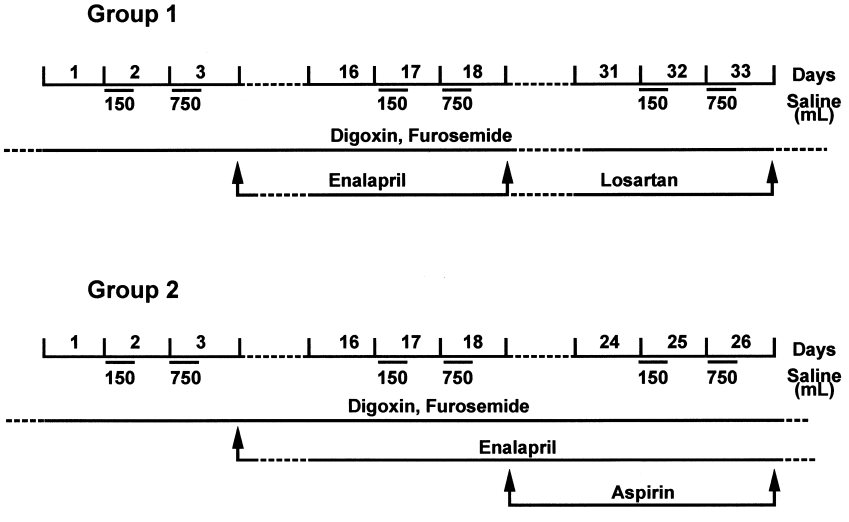

Figure 1. Study design.

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Table 1. Demographic, Clinical and Laboratory Baseline Variables in the Study Groups

	Group 1 (n = 20)	Group 2 (n = 9)
Age (yrs)	58 ± 11	57 ± 10
Gender M/F (n)	20/0	9/0
BSA (m^2)	1.90 ± 0.2	1.85 ± 0.3
SBP/DBP (mm Hg)	128 ± 8/80 ± 4	123 ± 7/80 ± 3
Serum creatinine (mg/dl)	1.10 ± 0.07	1.20 ± 0.07
FEV_1 (liters)	3.1 ± 0.6	2.9 ± 0.7
%Predicted	86 ± 10	85 ± 10
VC (liters)	3.5 ± 0.7	3.6 ± 0.7
%Predicted	78 ± 12	80 ± 12
TLC (liters)	4.9 ± 0.6	5.1 ± 0.8
%Predicted	79 ± 10	82 ± 9
Digoxin (mg/day)	0.25 ± 0.07	0.25 ± 0.04
Furosemide (mg/day)	70 ± 30	83 ± 30
DCO (ml/min per mm Hg)	22.5 ± 5.0	22.0 ± 7.0
%Predicted	79 ± 4	78 ± 5
DM (ml/min per mm Hg)	31 ± 5	30 ± 8
Vc′ (ml)	129 ± 20	128 ± 25
LVEF (%)	30 ± 5	32 ± 4
CI (ml/min per m^2)	2,347 ± 400	2,395 ± 400
Mean rap (mm Hg)	2.0 ± 1.4	1.0 ± 1.0
Mean WPP (mm Hg)	10.5 ± 3.8	10 ± 4
Urinary output (ml/24 h)	1,600 ± 200	1,550 ± 290
Urinary Na^+ excretion (mmol/24 h)	96 ± 5	101 ± 4
MR (subjective scale)	1.5 ± 0.1	1.7 ± 0.2

Data are presented as the mean value ± SD, except for gender.

BSA = body surface area; CI = cardiac index; DBP = diastolic blood pressure; DCO = pulmonary diffusing capacity for carbon monoxide; DM = alveolar-capillary membrane-diffusing capacity; FEV_1 = forced expiratory volume in 1s; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; Na = sodium; rap = right atrial pressure; SBP = systolic blood pressure; TLC = total lung capacity; Vc′ = pulmonary capillary blood volume; VC = vital capacity; WPP = wedge pulmonary pressure.

measurements of 1/DM, with a correlation coefficient of 0.96 and a coefficient of variation <6%.

Study design. All patients were kept on stable optimal doses of digoxin and furosemide, and none had signs of fluid retention. After the screening tests, patients in groups 1 and 2 were placed on a constant isocaloric diet containing 130 mmol Na^+, 90 mmol K^+ and 1500 ml water per day for the entire duration of the study. After five days of the controlled diet, patients in group 1 were admitted to the Heart Failure Unit, where confirmation of sodium balance was achieved with urinary Na^+, K^+ and creatinine monitoring in the first 24 h. The protocol included infusion of 0.9% sodium chloride solution in amounts of 150 ml (second 24 h) and 750 ml (third 24 h). Then, patients started receiving enalapril (20 mg/day) in addition to the baseline treatment, which was kept constant throughout the study period; they were discharged from the hospital and readmitted two weeks later for a repeat of the same procedures while continuing enalapril. Subsequently, losartan (50 mg/day) was substituted for enalapril, and the measurements were repeated after two weeks while continuing losartan. The first and second steps of the protocol in group 2 were similar to those in group 1. In patients in group 2, the third study step consisted of the combination of enalapril with aspirin (325 mg/day). After a week, saline infusions and gas transfer measurements were repeated with the same methods. The duration of the study in groups 1 and 2, the infusion sequences and the drug treatments are depicted in Figure 1. The investigators had no knowledge of the patients' clinical condition and treatment. Studies were begun at 8 AM after an overnight fast. A 5F triple-lumen, flow-directed, balloon-tipped thermodilution catheter was introduced percutaneously, under local anesthesia, into an antecubital vein and advanced to the pulmonary circulation under fluoroscopic guidance in a recumbent position. Then, the patient's chest wall was elevated at 45° in a comfortable position, which was maintained throughout the studies. For measurement of water and Na^+ excretion, urine was collected in the 3 h before and in the 3 h after saline infusion. Right atrial and wedge pulmonary pressures were monitored through each study. Saline infusions were made in the main stem of the pulmonary artery at a rate of 0.2 ml/kg per min. The DCO, DM and Vc′ values were determined twice in the 2 h before infusion, soon after infusion and 1 and 2 h later. Ten minutes before and after each infusion, mixed venous blood was withdrawn for measurements of hematocrit (HCT), hemoglobin, protein, aldosterone and norepinephrine (NE) plasma concentrations, as well as plasma renin activity (PRA). Cardiac output (thermodilution, average of two determinations) and LVEF were also measured. Pulmonary arteriolar resistance was calculated as mean pulmonary artery pressure − mean wedge pulmonary pressure × 1,332 × 60/cardiac output.

Laboratory methods. The severity of mitral regurgitation was assessed by color Doppler velocimetry and was graded

Table 2. Mean Baseline Values of Cardiac, Pulmonary, Hematologic and Humoral Variables in the Control Condition, During Enalapril and Losartan Treatment, and Their Average Percent Variations From Baseline Immediately After 150-ml and 750-ml Saline Infusions in Group 1 Patients

	150 ml Saline					
	Control		Enalapril		Losartan	
	Baseline	Δ%	Baseline	Δ%	Baseline	Δ%
LVEF (%)	30 ± 5.0	0.5 ± 0.1	33 ± 5.0	0.6 ± 0.2	31 ± 4.0	0.3 ± 0.2
CI (ml/min per m^2)	2,347 ± 400	2 ± 1.0	2,420 ± 500	4 ± 1.0	2,405 ± 350	5 ± 2.0
DM/VA (ml/min per mm Hg)	5.6 ± 3.0	−5.2 ± 4.0*	6.1 ± 3.0†	−5.5 ± 2.0*	5.5 ± 2.5	−5.4 ± 3.0*
HCT (%)	41 ± 4.0	−0.9 ± 0.2	39.1 ± 3.0	−0.2 ± 0.1	39.9 ± 4.0	−0.3 ± 0.2
Hb (g/dl)	13.7 ± 2.0	−0.9 ± 0.3	13.2 ± 1.5	−0.3 ± 0.2	13.5 ± 1.7	−0.5 ± 0.1
PPC (g/dl)	6.7 ± 3.0	0.2 ± 0.5	6.7 ± 2.0	1.5 ± 0.8	6.6 ± 2.5	0.7 ± 0.3
Aldosterone (pg/ml)	260 ± 50	−10.3 ± 7.0*	143 ± 45†	−7.7 ± 7.0*†	152 ± 39†	−6.2 ± 6.1*†
PRA (ng/ml per h)	5.0 ± 2.0	−14.5 ± 8.0*	9.9 ± 3.0†	−22 ± 9.0*†	10.2 ± 4.0†	−18.3 ± 7.0*†
NE (pg/ml)	440 ± 100	24 ± 15§	452 ± 90	−10 ± 8.0*†	405 ± 85	−13 ± 6.0*†
	750 ml Saline					
	Baseline	Δ%	Baseline	Δ%	Baseline	Δ%
LVEF (%)	32 ± 6.0	1.0 ± 0.3	35 ± 5.0	0.8 ± 0.2	33 ± 4.0	1.1 ± 0.8
CI (ml/min per m^2)	2,310 ± 380	3.0 ± 1.5	2,390 ± 350	5.0 ± 2.0	2,415 ± 270	4.0 ± 2.6
DM/VA (ml/min per mm Hg)	5.6 ± 2.0	−6.1 ± 4.0*	6.2 ± 2.0†	−6.3 ± 2.0*†	5.3 ± 2.1	−6.7 ± 3.0*
HCT (%)	40.4 ± 4.0	−5.5 ± 2.0*‡	39.6 ± 5.0	−7 ± 3.0*‡	41.1 ± 3.0	−8 ± 2.0*‡
Hb (g/dl)	13.6 ± 2.5	−5.7 ± 2.0*‡	13.2 ± 2.0	−5.2 ± 2.0*‡	13.5 ± 1.9	−5.8 ± 1.8*‡
PPC (g/dl)	6.6 ± 3.0	−5.7 ± 2.0*‡	6.6 ± 3.0	−6.0 ± 2.7*‡	6.6 ± 2.0	−5.9 ± 2.0*‡
Aldosterone (pg/ml)	251 ± 40	−35 ± 8*‡	140 ± 40†	−35.7 ± 9.0*‡	158 ± 32†	−30.4 ± 6.0*‡
PRA (ng/ml per h)	5.2 ± 2.0	−48 ± 15*‡	10.1 ± 4.0†	−28 ± 10*†	11 ± 3.1†	−33 ± 12*‡
NE (pg/ml)	450 ± 90	40 ± 15*‡	449 ± 85	−9 ± 4*†	397 ± 78	−15 ± 5.0*†

*$p < 0.01$ versus baseline. †$p < 0.01$ versus control condition. ‡$p < 0.01$ versus 150 ml saline. Data are presented as mean value ± SD.

Hb = hemoglobin; HCT = hematocrit; NE = norepinephrine; PPC = plasma protein concentration; PRA = plasma renin activity; VA = alveolar volume; other abbreviations as in Table 1.

subjectively on a scale from 0 (none) to 5 (severe). Two-dimensional echocardiography was the modality used to measure LVEF (Simpson's rule) at rest. Measurements of HCT were corrected for trapped plasma volume and for whole-body HCT. Aldosterone plasma concentration and PRA were determined by radioimmunoassay. Norepinephrine was measured by high performance liquid chromatography. Urine electrolytes were measured by ion-selective electrodes.

Statistical analysis. Data are expressed as the mean value ± SD. Statistical analysis was performed by using two-way repeated-measures analysis of variance, Newman-Keuls multiple comparison procedures (post hoc analysis was not performed unless analysis of variance reached statistical significance) and linear regression. A p value <0.05 was considered significant.

RESULTS

In groups 1 and 2, demographic data, blood pressure, renal function, urinary water and sodium excretion and drug treatments were comparable; right atrial and wedge pulmonary pressures at rest were within normal limits; cardiac index and LVEF were reduced; and forced expiratory volume in 1 s, vital and total lung capacities and DCO were lower than the predicted normal values (Table 1). In the two groups in the control condition, baseline HCT, hemoglobin and plasma protein concentrations were normal; baseline plasma aldosterone and NE concentrations and PRA exceeded normal values (Table 2). There were no significant differences in the pre-infusion data between sessions, both in the control condition and during drug treatment. No patient had symptoms or complaints during the studies.

In group 1, immediately after the 150-ml infusion, we recorded a significant reduction in aldosterone, PRA and DM/VA; a trend toward a slight decrease of HCT, hemoglobin and plasma protein concentrations; and a significant increase of NE (Table 2). We also recorded a decrease with saline of DCO and DM and an increase in Vc′ (Fig. 2). These responses were somewhat greater after the 750-ml solution and were not associated with variations in the cardiac index, LVEF (Table 2) or right atrial and pulmonary capillary wedge pressures (Fig. 2). After giving patients enalapril for two weeks, baseline aldosterone was lowered and PRA was raised, as compared with baseline values in the control condition. There was also some increase in the cardiac index, as well as a decrease in the pulmonary wedge pressure and arteriolar resistance; none of these variations, however, was significant. The DM/VA, DCO and DM values at rest were significantly augmented with enalapril, and the increase in DM did not show a relation with the effects on pulmonary arteriolar resistance. The percent decreases in DM/VA, DCO and DM with saline were unchanged as compared with those values before enalapril treatment (Fig. 3). Because of this, their absolute values reached after saline

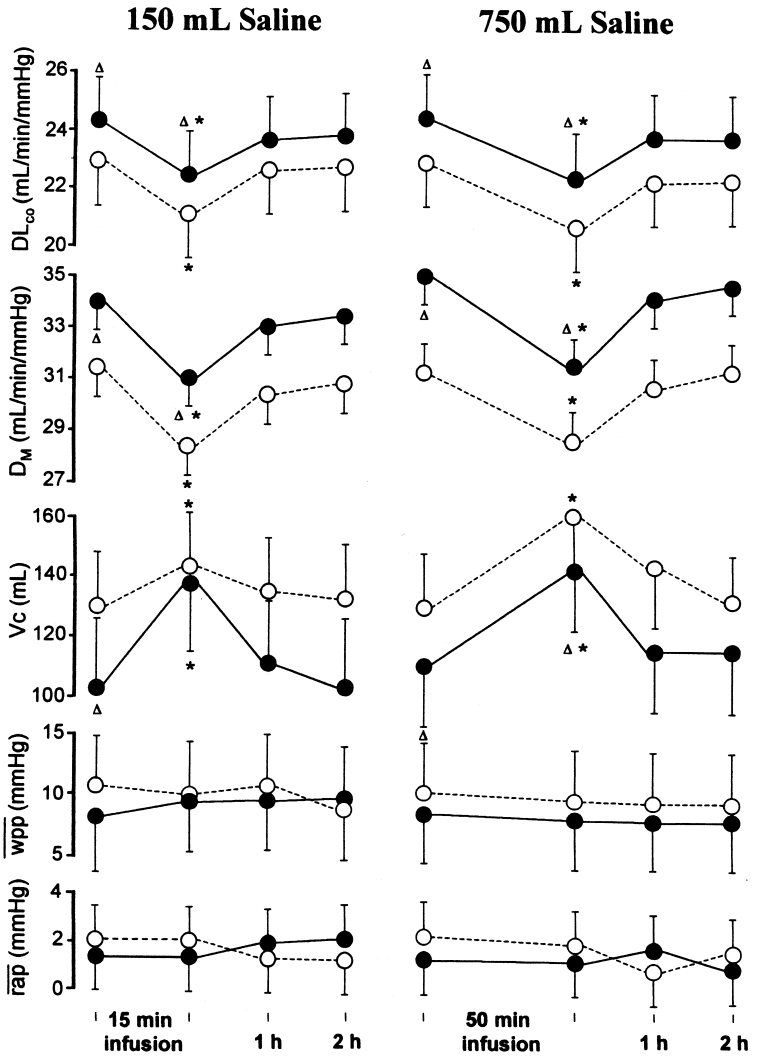

Figure 2. Pulmonary diffusion capacity for carbon monoxide (DCO), alveolar-capillary membrane-diffusing capacity (DM), pulmonary capillary blood volume (Vc′), mean wedge pulmonary pressure ($\overline{wpp}$) and mean right atrial pressure ($\overline{rap}$) in group 1 patients before and after 150-ml and 750-ml saline infusions in the absence **(open circles)** and presence **(solid circles)** of enalapril in the therapeutic regimen. *$p < 0.01$ vs. baseline. Δ$p < 0.01$ vs. corresponding value before enalapril treatment.

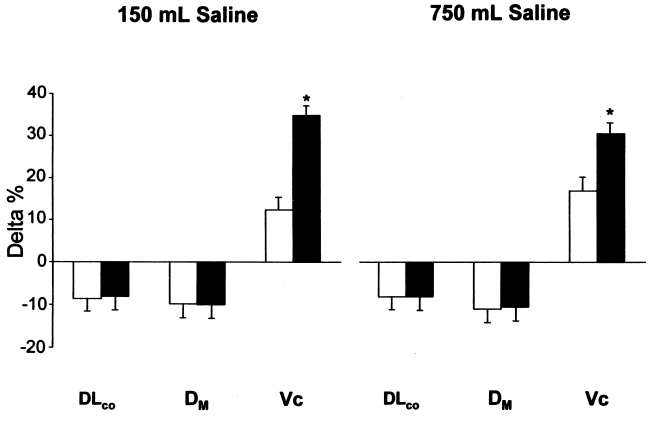

Figure 3. Respiratory average percent variations in group 1 patients from before to immediately after 150-ml and 750-ml saline infusions in the control condition **(open columns)** and after enalapril treatment **(solid bars)**. *$p < 0.01$ vs. control condition. Abbreviations as in Figure 2.

turned out to be significantly greater after than those before enalapril (Fig. 2). While the patients took enalapril, saline caused a greater increase of Vc′ (Fig. 2) and reduced plasma NE (Table 2). Right atrial and pulmonary capillary wedge pressures did not vary with saline. The time course of the pulmonary response was not affected by enalapril (Fig. 2).

After giving these same patients losartan for two weeks, baseline aldosterone was reduced and PRA was increased as compared with those values at baseline in the control condition; DM/VA, DCO and DM at rest reverted to values comparable to the control ones, and saline infusions brought them down to levels similar to those attained before enalapril. AT_1 receptor blockade was not effective on the time course of the pulmonary response to saline; during losartan treatment, right atrial and pulmonary wedge pressures did not vary significantly with infusion of saline (Table 2 and Fig. 4).

In group 2, the effects of the ACE inhibitor on the

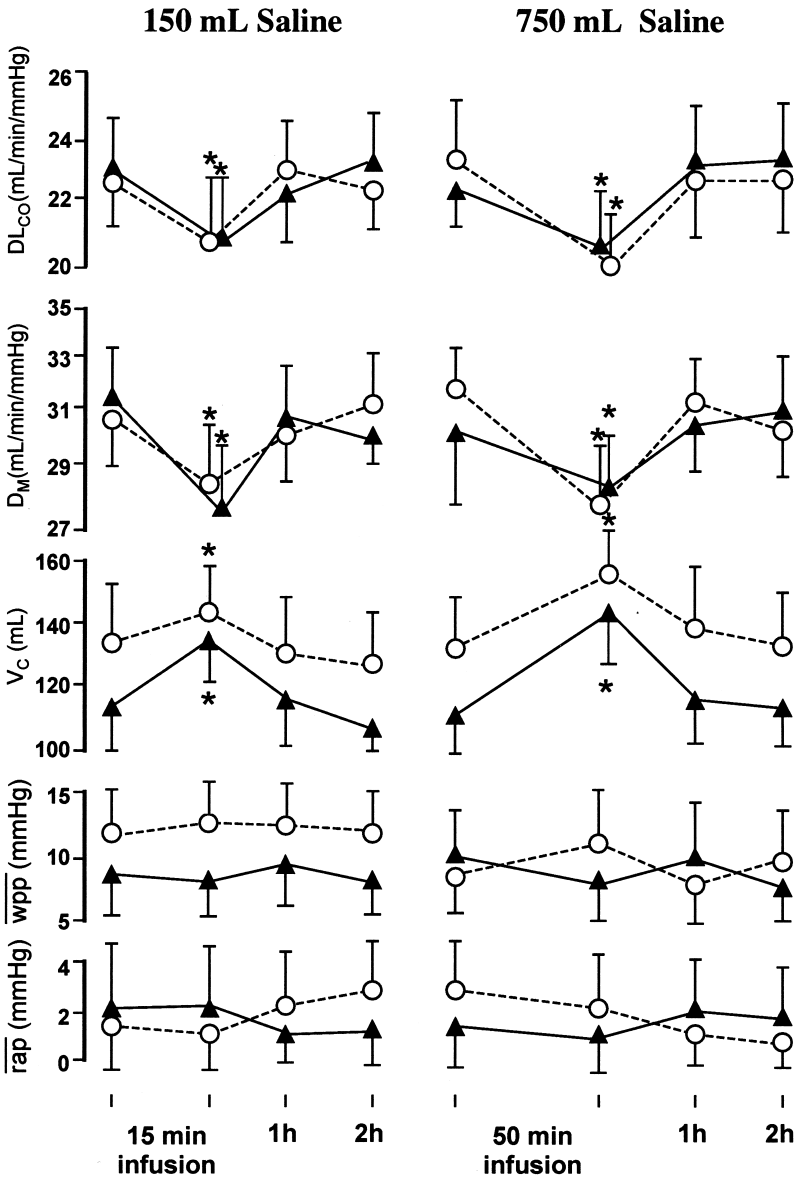

Figure 4. Pulmonary diffusion capacity for carbon monoxide (DCO), alveolar-capillary membrane-diffusing capacity (DM), pulmonary capillary blood volume (Vc′), mean wedge pulmonary pressure ($\overline{wpp}$) and mean right atrial pressure ($\overline{rap}$) in group 1 patients before and after 150-ml and 750-ml saline infusions in the absence **(open circles)** and presence **(solid triangles)** of losartan in the therapeutic regimen. *$p < 0.01$ vs. baseline.

examined variables at rest, as well as the response to saline, were comparable to those in group 1. With the combination of enalapril with aspirin, as compared with enalapril alone, there were no changes in the baseline cardiac index, LVEF, circulating NE or aldosterone; DCO, DM, DM/VA and Vc′ at rest and their responses to saline reverted to levels similar to the control ones (Fig. 5). The counteracting effect of aspirin resulted in abolition of the benefits of enalapril on the alveolar-capillary membrane gas transfer.

DISCUSSION

Angiotensin-converting enzyme inhibition was able to preserve the pulmonary gas transfer in patients with CHF, both at rest and when the alveolar-capillary membrane was challenged with a salt-mediated increase in diffusion resistance. Enalapril, in fact, augmented DCO, DM and DM/VA at rest. The percent depression of these variables with infusion of saline was similar in the presence and absence of ACE inhibition. A similar percent reduction of an increased value of DM suggests that the greater the improvement of DM at rest, the lower the influence of saline on diffusion resistance. According to this, absolute levels of DCO, DM and DM/VA reached during saline infusion were significantly higher than those before enalapril. AT_1 receptor blockade with losartan failed to provide the same results.

Effects of saline. We chose to infuse an amount of saline (150 ml) similar to the accepted value for pulmonary

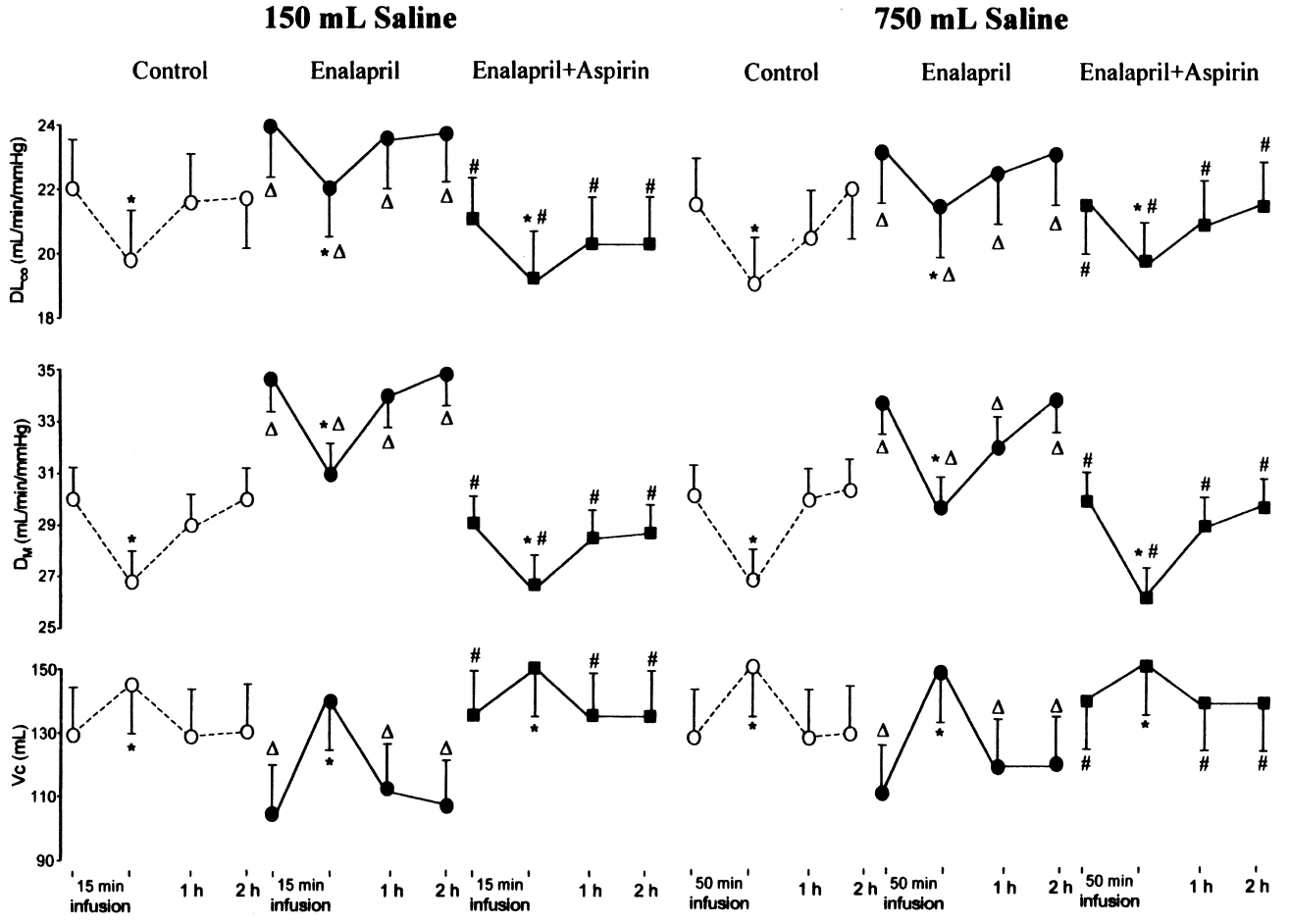

Figure 5. Pulmonary diffusion capacity for carbon monoxide (DCO), alveolar-capillary membrane-diffusing capacity (DM) and pulmonary capillary blood volume (Vc′) before and after 150-ml and 750-ml saline infusions in the control condition **(open circles)**, with enalapril alone **(solid circles)** and after combining aspirin with enalapril **(solid squares)**. *$p < 0.05$ vs. baseline. $\Delta p < 0.05$ vs. corresponding control value. #$p < 0.05$ vs. corresponding enalapril value.

capillary blood volume in humans in a supine position (18), as well as a fivefold greater amount. We reasoned that, because ACE inhibition and AT_1 receptor blockade interfere with the same hormones (PRA, aldosterone and NE) involved in the humoral reaction to saline, the use of different amounts of solution with different humoral-stimulating properties would bring greater understanding to the mechanisms of drug action.

Conditions causing an expansion in circulating volume, or movement of blood from the periphery to the thorax (19), are associated with an acute increase in Vc′, DM and DCO. In our patients, saline infusion produced an increase of the capillary blood volume available for gas exchange (Vc′), as well as a decrease in DCO, DM and DM/VA. An abrupt fall in DM suggests the development of acute changes in the membrane-diffusing properties. A number of factors make it likely that, in CHF, saline causes subclinical interstitial pulmonary edema, due to an upregulated sodium transport across the microvascular endothelium barrier, which results in DM being reduced: there were no changes in hydrostatic forces; the decrease in conductance was prompt and disappeared within less than 1 h; impedance to gas transfer presumably was greater than that gathered from the assessment of DM, because it was such as to overcome the opposing effects of increased Vc′; and the response to saline varied in parallel with the amount of solution infused, even though the relation was not linear. Possible reasons for this might be a greater rise in interstitial fluid pressure with a greater amount of saline, a dilution of interstitial proteins and increased lymph flow (20,21). Development of interstitial pulmonary edema would be expected to affect gas exchange by augmenting the thickness of the alveolar-capillary membrane, by reducing the compliance of alveoli and by compressing small blood vessels, resulting in non-uniform air flow and blood flow distribution.

Enalapril versus losartan. As to the process underlying the benefits of enalapril on gas conductance and the failure of losartan to provide the same results, the interpretations are more complex. Changes in aldosterone and NE do not seem to have a role because they were similar with the two drugs; with enalapril, DM improved at rest when aldosterone was reduced and NE was steady, and it worsened with saline when NE was inhibited and aldosterone was further diminished. These humoral changes were greater with the 750-ml

as compared with the 150-ml solution, but differences in the DM response to the two saline amounts were much smaller. A hypothetical participation of the enalapril-mediated adrenergic inhibition in the protection of gas diffusion (22) is inconsistent with the DM improvement with enalapril at rest, as it was not associated with changes in circulating NE. Although a loss of the gas transfer protective action of enalapril with aspirin in CHF has already been shown (3,10), we considered it important to demonstrate in this study that aspirin is adverse not only at rest but also under sodium challenge. This demonstration in group 2 suggests that vasodilating prostaglandins are a likely key mechanism for the protection of the alveolar-capillary function that enalapril exerts in either condition. Failure of the AT_1 receptor blocker conforms to this interpretation, as this drug category is devoid of significant prostanoid-stimulating properties.

Mechanisms of action. The answer to the basic question of whether the target of the prostaglandin action is the transport of sodium across the microvascular barrier is not an easy one. Considerations in favor of such a possibility include a fundamental role of prostaglandins in the preservation of endothelial integrity, capillary tone and permeability (23) and in the maintenance of normal pulmonary fluid conductance (24); and enhancement, instead of a reduction, of the gas diffusion with ACE inhibition (the greater Vc′ increase with saline infusion during enalapril treatment, in fact, may be expected to raise [25] the pulmonary microvascular pressure and fluid filtration). In a recent report (5), no measurable improvement of DCO and DM was seen in the first 48 h after starting enalapril, whereas a significant increase in these variables was apparent at studies repeated after a week. This might suggest that preservation of membrane gas transfer consists of a regression of the structural abnormalities through an inhibition of the angiotensin-mediated synthesis of collagen. Collagen has, in fact, a pivotal role in the cardiogenic stress failure of the alveolar-capillary barrier (1). This interpretation, however, is contradicted by the inefficacy of losartan. The hypothesis that collagen turnover is impeded through activation of the prostaglandin synthesis (26) implies the unconvincing possibility that structural improvement of the membrane with enalapril regresses within a week or less under the influence of aspirin. We therefore suggest that the balance of evidence argues in favor of a modulation, by enalapril, of an upregulated sodium transport across the pulmonary endothelium in patients with CHF. The increased hydrostatic load would be the initiator of the alveolar-capillary membrane stress failure (1), which, once developed, would persist (27), even if the stimulus is abolished by drug treatment or heart transplantation, and mediate a disordered salt and water metabolism.

Conclusions. Enalapril exerts a prostaglandin-mediated protective influence on alveolar-capillary membrane gas diffusion in patients with CHF, probably through a modulation of an upregulated sodium handling by the pulmonary microvascular endothelial barrier. Losartan does not share these properties. These notions are interesting in their own right, and possibly have wider clinical and therapeutic implications in this group of patients, in view of the peculiar exposure to the risk of salt retention.

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